

## A LOOK AT IODINE-INDUCED HYPERTHYROIDISM: RECOGNITION

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“**I**N spite of the volume of publication of the past hundred years, on the relation of iodine and goiter, medical opinion is still divided. Some doubt the existence of iod-Basedow (iodine-induced hyperthyroidism) while others class iodine, of which the body has daily need, as a poison.”<sup>1</sup> This pronouncement of de Quervain’s, made 35 years ago, freely translated, remains valid. With only a few dissidents, the scientific world relates endemic goiter and its concomitants, deaf-mutism and cretinism, to a lack of iodine. However, when widespread deficiencies are found and corrected, it come as a surprise if the populations under treatment for a time run an increased risk of hyperthyroidism. Apparently this complication has followed the recent use of large therapeutic or diagnostic doses. To review the highlights of the story seems worthwhile; it is intended neither to retrace the history of goiter nor to describe again the use of iodized salt. Nor is it proposed to challenge the small but important group which does not accept the unitary etiology of simple goiter,<sup>2</sup> whose members point out that in some heavily goitrous areas iodine is plentiful<sup>3</sup> and that neighboring groups with identical intake may show marked differences in the incidence of the disease.<sup>4</sup> Moreover, there are reports of well-studied outbreaks of goiter in which fluorides,<sup>5</sup> infectious agents,<sup>6</sup> or unidentified goitrogens<sup>7</sup> seem responsible. Nevertheless, control of the endemic disease has been synchronous with the introduction and popularization of iodine and, in time at least, complications have followed.

Early in 1820 Jean-François Coindet of Geneva reported that the recently discovered element, iodine, shrank goiter.<sup>8</sup> Born in 1774, he had received his M.D. at Edinburgh, and, returning to his native city, had become a successful practitioner. He had been elected M.R.C.P.,

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Edinburgh, and had won a French award for an essay on hydrocephalus. He was chief of medicine at both the civil and military hospitals of his city and a member of important community groups studying epidemic disease. His first paper was promptly republished in one Parisian and two Swiss scientific journals. Its impact must have been enormous.

As is often the case, others have claimed precedence. In 1834<sup>9</sup> William Prout of London asserted that, having proved on himself that potassium iodide is harmless, he had administered it in 1816 to a goitrous patient. "Striking effects of the remedy were observed" but he had lost track of the individual before "visual alterations." In 1819 he had recommended the drug to Dr. John Eliotson of St. Thomas's Hospital; the results are not recorded. J. C. Straub, a physician of Holwyl, discussed iodine at a scientific meeting in Bern in 1819. In an excellent recent review, Mach<sup>10</sup> intimates that Straub "was aware of the good results in 70 cases obtained by Dr. Irmiger of Zurich." These have not been found, nor are they mentioned in Straub's paper,<sup>11</sup> published early in 1820, in which sodium and calcium iodide are suggested as possible replacements for older antigoiter remedies but are not recommended. Straub's chief interest, based in part on the odor of the vapors, was the possible content of iodine in familiar substances other than sea sponge. Coindet's claim to fame seems secure. He made the essential synthesis: sponge ash cures goiter; it contains iodine; it should be taken undiluted. And thus he gave it.

For centuries goiter had been accepted in Switzerland and adjacent mountain regions as inevitable, as had its horrible concomitants, deaf-mutism and cretinism. While heredity and squalor were thought, perhaps rightly, to play some part in their etiology, and Coindet himself had called attention to the possible role of certain water supplies, treatment had had small success. Sea-sponge ash, recently found to contain iodine, had been used empirically since early time but had never become popular. Here was a *cure*; the thrill must have been like that at the birth of penicillin in the 1940s. According to the records of pharmacists, within a year more than 1,000 Genevans had taken iodine. But within months the Bibliothèque Universelle des Sciences, Belles Lettres et des Arts, which had published Coindet's first paper, warned that the remedy could be dangerous.<sup>12</sup> This admonition was certainly issued with his approval, since he was the medical editor. Early in

1821 Coindet's second paper<sup>13</sup> acknowledged that "annoying symptoms had been noted among prominent citizens" and that "a definite fear had been invoked against the use of iodine." By then he had treated 150 patients without difficulty, having chosen persons in robust health whose goiter was their only problem. These he had followed meticulously, discontinuing the use of the drug at the first sign of "iodism" (unspecified), or sooner if the tumor shrank or softened, the dosage being resumed after a suitable interval. This intermittance, he suggested, accounted for his success. When consulted by those whose treatment had been less guarded, he observed tremor, tachycardia, rapid loss of weight and strength despite increased appetite, and insomnia. The goiters had diminished in size. He attributed all this to "too fast an effect on the gland." To us it seems obviously to have been thyrotoxicosis. Publicly, he challenged the city's medical faculty to show that any of his own patients had suffered in this way.

His treatment of the unfortunate was to stop iodine, institute a diet of milk (preferably ass's milk), and to give warm baths and quieting drugs, including opium. If the goiter was hard or inflamed he applied leeches and warm fomentations locally. As a rule recovery was rapid. Since many of these untoward effects had followed overenthusiastic self-administered treatment, Coindet urged that pharmacists sell iodine only to patients who were under medical care. Soon this was ordered by the Council of State.<sup>14</sup> Coindet's own initial dose, whether of tincture or solution, contained approximately 250 mg. of iodine, but he often increased and even doubled this amount. The usual course of treatment was from eight to 20 days.

Prior to 1821 there are accounts of at least one instance which has been interpreted as hyperthyroidism following the treatment of goiter. In 1816 Augustin-Pyramide de Candolle, the famous Swiss botanist, began to have difficult breathing coincident with growth of a struma.<sup>15</sup> He consulted Coindet. After a second opinion had confirmed the nature of the problem, Coindet prescribed pills of sea-sponge ash, extract of saponaria, and extract of hemlock flower, not to be confused with the familiar tree. Dissatisfied with the slowness of his improvement, Candolle on his own tripled the dose for six weeks. In estimating his daily intake of iodine one must assume that von Fellenberg's iodine level of 0.39%<sup>16</sup> represents the concentration in sponge ash (it is not so defined), since several sources<sup>17</sup> give the concentration in what are generally

termed "bath sponges" at from 0.005 to 0.015%. Candolle then would have taken an average of about 0.6 gm. of iodine daily, approximately equivalent to 10 drops of saturated solution of potassium iodide morning and night. He fell gravely ill, the chief symptom being extreme anorexia, constant indigestion, and hallucinations; in addition, he lost weight and strength. This does not sound like hyperthyroidism. The toxicity of hemlock flower leaves is uncertain. The lethal alkaloid coniine is derived from the unripe fruit,<sup>18</sup> but saponaria yields nonabsorbable and irritant resins<sup>19</sup> which might have produced a gastric ulcer. Candolle returned for help to Coindet, who arranged a consultation with Jean-Louis Prévost, a relatively young man. Under the care of the latter, Candolle recovered in four or five months and lived, apparently in good health, until 1841, when he died at the age of 63.

There must have been alarm indeed in Geneva. For analogy, one might imagine that in 1927, less than a year after Minot and Murphy's announcement<sup>20</sup> of the liver diet for pernicious anemia, the *Boston Medical and Surgical Journal* had warned against it editorially, and this had been followed by an admission from its sponsors that the cure carried a risk of severe polycythemia! But a few months later Coindet thought he had solved the problem.<sup>21</sup> He reasoned that the untoward effects had come from the digestive tract, whereas the object was incorporation of iodine into the "lymphatic system." Accordingly, he advised rubbing a nut-sized morsel of approximately 5% potassium iodide in pork fat twice daily into goiters, scrofulous glands, or enlarged breasts; he had had excellent results in 22 cases. But he now "hedged his bets;" he not only maintained close surveillance, but in this, his third and apparently last publication on goiter, leeches and fomentations were a regular part of the treatment. However, he remained convinced of the value of iodine, using small doses in nongoitrous scrofula (presumably indolent tuberculosis of the cervical glands), and he suggested adding iodine to the usual mercurial treatment of syphilis, antedating Wallace of Dublin, who is generally credited with the first systematic use of iodides in the tertiary stage. While denying that iodine was a universal panacea, he endorsed its use in many diseases.

The use of iodine and its salts was quickly taken up by physicians on both sides of the Atlantic. Dupuytren praised it unreservedly:<sup>22</sup> "... (si) l'iode (soit) employé avec aucune sorte de fureur, aucun goitre ne resistait." Although Prévost administered it frequently in Geneva,

he noted some "ill-effects" with Coindet's dosage, and reduced it sharply.<sup>23</sup> Wallace noted<sup>24</sup> only occasional indigestion; he mentioned that Lugol had had difficulties with heavier dosages. Lugol eventually described 31 different prescriptions for iodine or iodides, including several for baths, but these were chiefly for skin diseases, most of which he lumped together as "scrofula."<sup>25</sup> Samuel Hobson of Philadelphia won the 1830-1831 prize of the Medical Society of the State of New York with an essay titled "The History, Preparations and Therapeutic Use of Iodine." In addition to bronchocele, he advised it for scrofula, syphilis, gout, affections of the liver or spleen, enlargement of the breasts or testes, and delayed menses. He considered the drug valueless in tuberculosis. He did not mention reactions.<sup>26</sup>

Evidence soon appeared that the incidence of goiter paralleled the lack of iodine in water, soil, or food—leading to the idea that prophylaxis was feasible. Boussingault,<sup>27</sup> a French geologist and chemist who worked for a British gold-mining company in what is now the Republic of Colombia, saw the "happiest results" in the prevention of goiter in native villages which for centuries had used iodized salt, compared with others using a "purified" product. He added that large doses of iodine had provoked (unspecified) troubles. On his return to France he advised that sea salt or modified salt (KI 1:10,000) be given to inhabitants of goitrous areas. Köstl<sup>28</sup> asserted that 100,000 cases of goiter had been prevented, largely in the province of Styria, Austria. He felt the additional cost should somehow be spared the consumer. Chatin, a leader of French chemistry, determined the quantity of iodine in soil, water, and food in goitrous and nongoitrous districts, finding these to be inversely proportional to the severity of the endemic disease.<sup>29</sup> Thus he anticipated Fellenberg and McClendon. Although in recent years the laboratory determination of small quantities of iodine has required stringent safeguards against contamination, the sources thereof were probably fewer at that time, and the direction of Chatin's results appears to have been significant. If, he concluded, foods were chosen for their content of iodine, supplements would be unnecessary. Minute amounts of iodine would suffice; he said that he had seen "cures" of goiter from the use of mineral water which contained no more than 0.1 mg. per liter; the amounts consumed were not recorded.

By 1860 prophylactic iodide was in use in several French departments and in some Austrian and Italian provinces.<sup>30</sup> Among the ill

## APPROXIMATE DAILY INTAKE OF IODINE

<i>Observer</i>	<i>Purpose</i>	<i>Amount (gm.)</i>	<i>Result</i>
J.-F. Coindet	Treatment of goiter	0.2 to 0.4	Safe
J. L. Prévost	Treatment of goiter	0.0009 to 0.002	Maximal safe dose
G. A. Chatin	Treatment of goiter	0.0001 to 0.0003	Minimal effective dose
A. Boinet	Treatment of goiter	0.15	Safe
F. Rilliet	Treatment of goiter	0.0008	Unsafe
J. B. J. D. Boussingault	Prophylaxis	0.0008	Safe
F. Köstl	Prophylaxis	0.0008	Safe
W. Wallace	Tertiary syphilis	0.45	Safe
J. G. A. H. Lugol	Miscellaneous non- goitrous diseases	0.125 to 0.375	Safe
S. S. Hobson	Miscellaneous non- goitrous diseases	0.12	Safe

effects encountered—besides the familiar reactions in the skin, mucous membranes, salivary glands, and stomach—there were probably cases of hyperthyroidism. These were usually attributed to the far larger therapeutic doses. However, in 1858 Rilliet of Geneva startled the Parisian and then the entire European medical establishment.<sup>31</sup> In an effort to show that small doses were innocuous, he had encouraged patients to use iodized salt (1:10,000) at the table, but symptoms had followed which appear to have been those of hyperthyroidism. Recovery followed the cessation of iodine, a diet of mare's milk, and the ingestion of iron; but at least one victim had a recurrence merely from staying at the sea shore. This person recovered promptly on his return to Geneva! It is probable that these patients of Rilliet's were all goitrous and over the age of 40.

The Imperial Academy of Medicine in Paris, to which Rilliet's first paper was read, promptly appointed a committee, with Trousseau as chairman, to investigate and report on the topic. The discussion rolled on for months<sup>32</sup> and involved most of the Parisian scientific world. Trousseau was skeptical; he wondered whether, since "constitutional iodism" occurred only in the goitrous, they might be predisposed to it. Or perhaps these were cases of naturally occurring Basedow's disease, as it then was called. Velpeau challenged the validity of Rilliet's observations, which depended on only four cases, and Boinet<sup>33</sup> maintained that prophylaxis with natural iodine-containing foods was safe

and advisable, although he at times prescribed the tincture. There was dispute about the relative iodine content of atmosphere and of water in Paris and Geneva. Chatin finally threw his weight behind Rilliet. Ricord concluded his discussion by reminding the Academy that Paris was safe. Why go to Geneva?

The warning note had been sounded. If minute doses of potassium iodide (0.001 gm./day) were dangerous, one had best take care. As in Geneva 40 years earlier, "a definite fear had been invoked against the use of iodine." There was no agreement on a safe dose; the syphilographers prescribed grams, while Rilliet and d'Espine warned against milligrams (see the accompanying table). This incongruity, of course, may have depended on different subjects, nongoitrous or goitrous. If we scan the so-called toxic reactions to iodine reported in the years 1850 to 1900,<sup>34</sup> we can readily identify cutaneous syndromes and a few bizarre entities, but there remains a considerable body of what may have been postiodine hyperthyroidism. Trousseau applied the term "*goiter exophthalmique*" in 1868,<sup>35</sup> but the century had to await Breuer's two papers<sup>36</sup> to establish iod-Basedow as an entity which would arouse the interest and apprehension of the great Swiss goiter surgeons.

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